current and future treatments of spinal muscular atrophy

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this commentary is on the original article by aragon-gawinska et al. on pages 310–314 of this issue.

spinal muscular atrophy (SMA) arises in 95% of cases from homozygous deletions or point mutations in the survival motor neuron 1 (SMN1) gene and has historically been an incurable illness. Traditionally it is divided into three main groups, depending on functional ability: unable to sit (type I); able to sit but not stand (type II); and able to walk (type III). Type I has always seemed to me a particularly bleak diagnosis, with the natural history of an alert child who would succumb to respiratory failure within early infancy, and long-term ventilation with almost total paralysis the only unpalatable alternative until very recently.

I recall similar feelings of futility when working as a young doctor in the early 1990s with HIV-positive individuals who had progressed to AIDS. Thankfully, the prognosis for HIV has been revolutionized in the meantime, and it is hugely encouraging that treatments to challenge the natural history of SMA are now a reality. The first drug to be widely used in clinical practice is nusinersen, an antisense oligonucleotide therapy designed to modify SMN2 mRNA splicing to increase the amount of functional SMN protein.

Nevertheless, we are still a long way from the summit. Aragon-Gawinska et al.2 have given us a very clear guide to how far we have climbed so far. The take-home message from their study of 47 nusinersen-treated individuals with SMA1 is that one-third were able to sit unsupported at 14 months after commencement of therapy. The main factors which influenced whether or not sitting was attained were the condition at baseline and clinical response over the first 6 months. Interestingly, the number of copies of SMN2 was not correlated with a better outcome, despite the association between milder disease in those with more copies of SMN2.

It is tempting to strike a sober tone, noting that only a minority reach sitting and, even for those individuals, SMA is likely to remain life limiting. The drug is costly and requires intrathecal administration. I am aware of families who have elected not to take this option, viewing it as merely prolonging suffering. Nevertheless, in an echo of the HIV story, I cannot help but feel optimistic that we are on a journey to very substantially changing the lives of these children.

The immediate horizon is full of further novel drugs under development (many of which can be administered orally or intravenously), that may supersede current therapy or at least prove stepping stones to more substantial breakthroughs. In 2019 Schorling et al.3 divided these into four main strategies: (1) SMN1 gene replacement, e.g. AVXS-101 (Zolgensma); (2) SMN2 gene enhancement, e.g. nusinersen, RG7916 (Risdiplam), and LMI070 (Brana- plam); (3) muscle protection, e.g. CK-2127107 (Reldesem- tiv) and SRK-015; and (4) motor neuron protection, e.g. Olesoxime.

Intuitively, it seems appropriate that therapy should be started as early as possible (ideally when asymptomatic) and the benefit of screening newborn infants for SMA seems increasingly persuasive. This is now widely available in the US but not in the UK, despite support from a majority in the community of families and adults affected by SMA and the general public.4,5 Currently available techniques are not able to predict phenotype; but as there is a common genotype and all therapies available or under development have the potential to benefit all phenotypes, this is not obviously a major concern.

REFERENCES